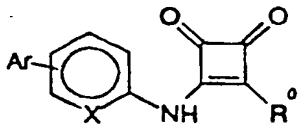




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<p>(21) International Application Number: PCT/EP94/01921 (22) International Filing Date: 7 June 1994 (07.06.94) (30) Priority Data: 9312210.9 14 June 1993 (14.06.93) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): COATES, William, John [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). RAWLINGS, Derek, Anthony [GB/GB]; SmithKline Beecham Pharmaceuticals, The Frythe, Welwyn, Hertfordshire AL6 9AR (GB). (74) Agent: THOMPSON, Clive, B.; Corporate Intellectual Property, SmithKline Beecham, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).</p>		<p>(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  Published With international search report.</p>
<p>(54) Title: AMILINO- OR PYRIDYLAMINO- CYCLOBUTENE- 1,2-DIONE DERIVATIVES AS cGMP PHOSPHODIESTERASE INHIBITORS</p> <p>(57) Abstract</p> <p>A compound of formula (1) or a pharmaceutically acceptable salt thereof, wherein Ar is an optionally substituted aryl or heteroaryl ring selected from phenyl, naphthyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, imidazolyl, thienyl, oxazolyl, benzimidazolyl, benzoxazolyl, indolyl or thianaphthenyl, X is CH or N; R<sup>0</sup> is NR<sup>1</sup>R<sup>2</sup> or hydrogen; and R<sup>1</sup> and R<sup>2</sup> are independently hydrogen or C<sub>1</sub>-alkyl. The compounds of this invention are inhibitors of calmodulin insensitive cyclic GMP phosphodiesterase and are of use in combating such conditions where such inhibition is thought to be beneficial.</p> <div style="text-align: center;">  <p>(1)</p> </div>		

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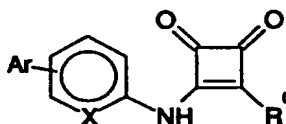
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Aminino- or pyridylamino- cyclobutene- 1,2-dione derivatives as cGMP phosphodiesterase inhibitors

The present invention relates to dioxocyclobutene derivatives, processes for their preparation, intermediates in their preparation, their use as therapeutic agents and to pharmaceutical compositions containing them. The compounds of this invention are inhibitors of a calmodulin insensitive cyclic GMP phosphodiesterase and are of use in combating such conditions where such inhibition is thought to be beneficial. They are bronchodilators and are therefore of use in combating chronic reversible obstructive lung diseases such as asthma and bronchitis. Some of the compounds of the present invention have anti-allergic activity and are therefore useful in combating allergic diseases such as allergic asthma, allergic rhinitis, urticaria and gastrointestinal motility disorders such as irritable bowel syndrome. Furthermore the compounds of this invention are vasodilators and are therefore of value in combating angina, hypertension and congestive heart failure. Also the compounds of this invention are smooth muscle relaxants and are therefore of value in treating male sexual dysfunction, e.g. impotence.

Accordingly the present invention provides compounds of the formula (1) :



Formula (1)

and pharmaceutically acceptable salts thereof, wherein

Ar is an optionally substituted aryl or heteroaryl ring selected from phenyl, naphthyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, imidazolyl, thienyl, oxazolyl, benzimidazolyl, benzoxazolyl, indolyl or thianaphthenyl,

X is CH or N;

R<sup>0</sup> is NR<sup>1</sup>R<sup>2</sup> or hydrogen; and

R<sup>1</sup> and R<sup>2</sup> are independently hydrogen or C<sub>1-6</sub>alkyl.

Suitably Ar is phenyl.

Suitably Ar is 2-,3- or 4-pyridyl, 5-pyrimidyl, 2- or 4-imidazolyl, 2- or 3-thienyl, 2-oxazolyl, 2-benzimidazolyl, 2-benzoxazolyl, 2-indolyl or 2-thianaphthenyl.

Preferred heteroaryl rings include 3-pyridyl, 2-thiophenyl or 2-indolyl

Suitably Ar is unsubstituted or substituted by at least one group selected from

C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy or hydroxy.

Suitably Ar is positioned ortho- or meta- to X.

Suitably X is CH.

Suitably R<sup>0</sup> is NR<sup>1</sup>R<sup>2</sup>.

Suitably R<sup>1</sup> is hydrogen and R<sup>2</sup> is hydrogen or C<sub>1-6</sub>alkyl.

Preferably R<sup>1</sup> and R<sup>2</sup> are both hydrogen.

- 5        Examples of C<sub>1-6</sub>alkyl groups include methyl, ethyl, propyl, butyl, pentyl and hexyl, preferably methyl.

Particular compounds of this invention include :

- 3-amino-4-[4-(3-pyridyl)]anilino-3-cyclobutene-1,2-dione,  
 3-amino-4-[3-(4-imidazolyl)anilino]-3-cyclobutene-1,2-dione,  
 10    3-methylamino-4-[3-(5-methyl-4-imidazolyl)anilino]-3-cyclobutene-1,2-dione,  
 3-dimethylamino-4-[3-(5-methyl-4-imidazolyl)anilino]-3-cyclobutene-1,2-dione,  
 3-amino-4-[3-(3-methyl-4-pyridyl)anilino]-3-cyclobutene-1,2-dione,  
 3-amino-4-[3-(2-oxazolyl)anilino]-3-cyclobutene-1,2-dione,  
 3-amino-4-[3-(4-pyridyl)anilino]-3-cyclobutene-1,2-dione,  
 15    3-amino-4-[3-(3-pyridyl)anilino]-3-cyclobutene-1,2-dione,  
 3-amino-4-[3-(2-pyridyl)anilino]-3-cyclobutene-1,2-dione,  
 3-amino-4-[3-(2-thienyl)anilino]-3-cyclobutene-1,2-dione,  
 3-amino-4-[3-(3-thienyl)anilino]-3-cyclobutene-1,2-dione,  
 3-amino-4-[3-(2-thianaphthene)anilino]-3-cyclobutene-1,2-dione,  
 20    3-amino-4-[3-(5-pyrimidyl)anilino]-3-cyclobutene-1,2-dione,  
 3-amino-4-[3-(2-benzoxazolyl)anilino]-3-cyclobutene-1,2-dione,  
 3-amino-4-[3-(2-benzimidazolyl)anilino]-3-cyclobutene-1,2-dione,  
 3-amino-4-[3-(2-indolyl)anilino]-3-cyclobutene-1,2-dione,  
 3-amino-4-(3-phenyl)anilino-3-cyclobutene-1,2-dione,  
 25    3-amino-4-[3-(2-hydroxyphenyl)anilino]-3-cyclobutene-1,2-dione,  
 3-amino-4-[3-(2-methoxyphenyl)anilino]-3-cyclobutene-1,2-dione,  
 3-amino-4-[3-(3-hydroxy-2-pyridyl)anilino]-3-cyclobutene-1,2-dione,  
 3-amino-4-[3-(2-imidazolyl)anilino]-3-cyclobutene-1,2-dione,  
 3-amino-4-[6-(4-pyridyl)-2-pyridylamino]-3-cyclobutene-1,2-dione, and  
 30    3-[3-(4-pyridyl)anilino]-3-cyclobutene-1,2-dione,

or pharmaceutically acceptable salts thereof.

Compounds of the formula (1) may form pharmaceutically acceptable salts with acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acids.

Compounds of the formula (1) may form pharmaceutically acceptable salts with metal ions, such as alkali metals for example sodium and potassium, or with an ammonium ion.

In order to use a compound of the formula (1) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of formula (1) and their pharmaceutically acceptable salts may be administered in standard manner for the treatment of the indicated diseases, for example orally, parenterally, transdermally, rectally, via inhalation or via buccal administration.

Compounds of formula (1) and their pharmaceutically acceptable salts which are active when given orally or via buccal administration can be formulated as liquids, syrups, tablets, capsules and lozenges. An oral liquid formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include starch, celluloses, lactose, sucrose and magnesium stearate. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinyl-pyrrolidone, lecithin, arachis oil, or sesame oil.

A typical suppository formulation comprises a compound of formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered in the form of an aerosol using a conventional

propellant such as dichlorodifluoromethane or trichlorofluoromethane, or are in the form of a powder for insufflation.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

5 Each dosage unit for oral administration contains suitably from 0.001 mg/Kg to 30 mg/Kg, and preferably from 0.005 mg/Kg to 15 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.001 mg/Kg to 10 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base.

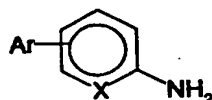
10 The daily dosage regimen for oral administration is suitably about 0.001 mg/Kg to 120 mg/Kg, of a compound of formula (1) or a pharmaceutically acceptable salt thereof calculated as the free base. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, for example about 0.005 mg/Kg to 10 mg/Kg, of a compound of the formula (1) or a pharmaceutically acceptable salt thereof calculated  
15 as the free base. The active ingredient may be administered as required for example from 1 to 8 times a day or by infusion. The compositions of the invention are bronchodilators and are useful in chronic reversible obstructive lung disease for example asthma and bronchitis. In addition some of the compositions of the present invention have anti-allergic activity and are useful in combating allergic diseases such as allergic asthma,  
20 allergic rhinitis, urticaria and irritable bowel syndrome. The compositions of the present invention also have vasodilator activity and are of use in the treatment of angina, hypertension and congestive heart failure. Such conditions can be treated by administration orally, topically, rectally, parenterally or by inhalation.

For administration by inhalation dosages are controlled by a valve, are  
25 administered as required and for an adult are conveniently in the range 0.1-5.0 mg of a compound of the formula (1) or a pharmaceutically acceptable salt thereof.

The compounds of this invention may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially. Conveniently the compounds of this invention and the other active  
30 compound or compounds are formulated in a pharmaceutical composition. Examples of compounds which may be included in pharmaceutical compositions with the compounds of the formula (1) are bronchodilators such as sympathomimetic amines for example isoprenaline, isoetharine, salbutamol, phenylephrine and ephedrine or xanthine derivatives for example theophylline and aminophylline, anti-allergic agents for example disodium  
35 cromoglycate, histamine H<sub>1</sub>-antagonists, vasodilators for example hydralazine, angiotensin converting enzyme inhibitors for example captopril, anti-anginal agents for example isosorbide nitrate, glyceryl trinitrate and pentaerythritol tetranitrate, anti-arrhythmic agents for example quinidine, procainamide and lignocaine, calcium antagonists for example

verapamil and nifedipine, diuretics such as thiazides and related compounds for example bendrofluazide, chlorothiazide, chlorothalidone, hydrochlorothiazide, and other diuretics for example frusemide and triamterene, and sedatives for example nitrazepam, flurazepam and diazepam.

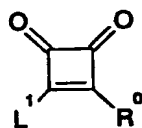
- 5 In another aspect the present invention provides a process for the preparation of compounds of the formula (1) or pharmaceutically acceptable salts thereof, which process comprises reacting a compound of the formula (2) :



10

Formula (2)

with a compound of the formula (3) :



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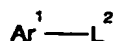
Formula (3)

- 20 wherein Ar, X and R<sup>0</sup> are as hereinbefore defined and L<sup>1</sup> is a leaving group, and thereafter optionally forming a pharmaceutically acceptable salt thereof.

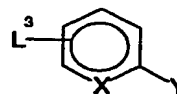
Suitably L<sup>1</sup> is C<sub>1-6</sub>alkoxy, halo or C<sub>1-6</sub>alkylthio, for examples methoxy, ethoxy, propoxy or n-butoxy. The reaction may be performed in the absence of a solvent or in a solvent such as a C<sub>1-4</sub>alkanol (e.g. methanol or ethanol), acetonitrile or pyridine at ambient or elevated temperature such as 30 to 160°C, conveniently at reflux temperature

25 when in the presence of a solvent.

Compounds of the formula (2) are known or may be prepared by standard methods. For example a compound of the formula (2) may be prepared by reacting in the presence of a palladium catalyst a compound of the formula (4) with a compound of the formula (5) :



Formula (4)



Formula (5)

wherein one of  $\text{L}^2$  and  $\text{L}^3$  is  $\text{B}(\text{OH})_2$  and the other is a suitable leaving group, Y is amino or a precursor thereof,  $\text{Ar}^1$  is a group Ar as hereinbefore defined or a precursor thereof and X is as hereinbefore defined, and thereafter if necessary :

- converting a group Y to amino
- 5 • converting a group  $\text{Ar}^1$  to Ar.

A suitable leaving group for  $\text{L}^2$  or  $\text{L}^3$  is halo, preferably bromo or trifluoromethanesulphonate. Preferably  $\text{L}^3$  is  $\text{B}(\text{OH})_2$ . Suitably the reaction of a compound of the formula (4) with a compound of the formula (5) is performed in the presence of a base such as triethylamine, barium hydroxide, sodium carbonate or sodium bicarbonate, and when  $\text{L}^2$  or  $\text{L}^3$  is trifluoromethanesulphonate in the presence of lithium chloride, in a solvent such as dimethoxyethane, tetrahydrofuran, benzene, ethanol, water or mixtures thereof, at elevated temperature (e.g. 30-150°C) preferably at the reflux temperature of the reaction mixture.

An example of a precursor of an amino group is a nitro group which can be reduced to an amino group in conventional manner, e.g. by catalytic hydrogenation. An alternative precursor is a protected amino group such as phthalamido which can be deprotected in conventional manner.

An example of a precursor of the group Ar is when Ar is substituted by an optionally substituted benzyloxy group such as 4-methoxybenzyloxy which can be converted to Ar substituted by hydroxy in conventional manner, e.g. by catalytic hydrogenation.

Compounds of the formula (3) are known or can be prepared by standard methods (e.g. as described in UK patent 1563090).

Compounds of the formulae (4) and (5) are known or may be prepared by standard methods.

Pharmaceutically acceptable acid addition salts of the compounds of the formula (1) may be prepared from the corresponding base of the compounds of the formula (1) in conventional manner. For example the base may be reacted with an acid in a  $\text{C}_{1-4}$ alkanol, or an ion-exchange resin may be used. The salts of the compounds of the formula (1) may be inter converted using ion-exchange resins. Non-pharmaceutically acceptable salts are therefore of use as they can be converted to pharmaceutically acceptable salts.



Pharmaceutically acceptable base addition salts of the compounds of the formula (1) may be prepared by standard methods, for example by reacting a solution of the compound of the formula (1) with a solution of the base.

The following biological test methods, data and Examples serve to illustrate this invention.

#### Bronchodilatation - In vivo

Male guinea-pigs of the Dunkin Hartley strain (500 - 600g) are anaesthetised with Sagatal (pentobarbital sodium) (60 mg/kg). Airway resistance is measured using a modification of the classical Konzett-Rossler technique (J. Pharm. Methods, 13, 309-315, 1985). U46619 (9,11-methanoepoxy-PGH<sub>2</sub>) is infused i.v. at a rate of 2.5 nmol/min, this produced a steady state of bronchoconstriction (approximately 120% increase from basal airway resistance). The compound under test is administered by i.v. bolus injection, and the subsequent peak inhibition of bronchoconstriction is recorded.

The dose of compound required to reduce the U46619-induced bronchoconstriction by 50% is given as the BD<sub>50</sub>.

#### Anti-allergic activity

Male Duncan Hartley guinea-pigs (250-300 g) are sensitised to ovalbumen by i.p. injection of 2 ml of 50 mg.ml<sup>-1</sup> i.p. and 0.2 ml s.c. Three weeks later they are anaesthetised with 60 mg.kg<sup>-1</sup> sodium pentobarbitone. The trachea is cannulated and the animal respires at a rate of 40 breaths per minute and at an initial tracheal inflation pressure of 16 mmHg. Tracheal inflation pressure is measured by a transducer connected to a side arm of the respiration circuit. The carotid artery is cannulated for the measurement of blood pressure and the signal is used to trigger an instantaneous rate meter. A jugular vein is cannulated for the administration of drug and allergen. After surgery the animals are allowed to stabilise and the drug is administered i.v. as a bolus. Following this, ovalbumen 1mg.kg<sup>-1</sup> is injected i.v. as the antigen challenge either 2, 15 or 30 minutes following drug treatment and the peak bronchoconstrictor response recorded. For the control group ovalbumen only is given. One ovalbumen challenge per guinea-pig is used and n = 6 for each time point. The percentage increase in tracheal inflation pressure is calculated.

#### Phosphodiesterase activity

The activity of the compounds of the present invention as inhibitors of a calmodulin insensitive cyclic GMP phosphodiesterase is measured using the procedure described in European Patent Application No. 293063. The concentration of compound

which inhibits the enzyme by 50% is given as the  $IC_{50}$  ( $\mu M$ ). The compounds of Examples 2, 5 to 11, 13 to 16, 18, 20 and 23 had  $IC_{50}$  values in the range 6 to 110  $\mu M$ .

### **Inhibition of Spontaneous Contraction in Guinea-Pig Colon**

Segments of isolated guinea-pig colon (2 cm) are suspended under 2 g tension in standard organ baths containing Krebs solution. The tissues are connected at the free end to isometric transducers which allow recording and display of developed tension on chart recorders. On-line computer capture and analysis are used to quantify the effects of test compounds on spontaneous contractions. Inhibitory responses are calculated as % maximum inhibition of spontaneous contraction distance over 3 consecutive pre and post dose 2 minute readings. The concentration of compound which causes 50% inhibition of the spontaneous contraction is given as the  $EC_{50}$  ( $\mu M$ ).

#### **Example 1**

##### **3-Amino-4-[4-(3-pyridyl)]anilino-3-cyclobutene-1,2-dione**

A solution of 3-(4-aminophenyl)pyridine (0.51 g) and 3-amino-4-ethoxy-3-cyclobutene-1,2-dione (0.42 g) in pyridine (2 ml) was stirred at 80° for 20 hours. The cool mixture was treated with water (15 ml) and the solid filtered off and washed with water and hot methanol. Recrystallation from dimethylformamide gave 0.33 g of the title compound, mp 322-4°C dec.

#### **Example 2**

##### **3-Amino-4-[3-(4-imidazolyl)anilino]-3-cyclobutene-1,2-dione**

In a manner similar to that of Example 1, 4-(3-aminophenyl)imidazole (0.48 g) and 3-amino-4-ethoxy-3-cyclobutene-1,2-dione (0.42 g) gave 0.40 g of the title compound, mp darkens ca. 300°C (from dimethylformamide/water).

#### **Example 3**

##### **3-Methylamino-4-[3-(5-methyl-4-imidazolyl)anilino]-3-cyclobutene-1,2-dione**

In a manner similar to that of Example 1, 4-(3-aminophenyl)-5-methylimidazole (0.43 g) and 3-ethoxy-4-methylamino-3-cyclobutene-1,2-dione (0.39 g) gave 0.36 g of the title compound, mp >330°C (from dimethylformamide).

**Example 4****3-Dimethylamino-4-[3-(5-methyl-4-imidazolyl)anilino]-3-cyclobutene-1,2-dione**

In a manner similar to that of Example 1, 4-(3-aminophenyl)-5-methyl-imidazole (0.57 g) and 3-dimethylamino-4-ethoxy-3-cyclobutene-1,2-dione (0.56 g) gave 0.34 g of the title compound, mp 290-292°C (from methanol).

**Example 5****3-Amino-4-[3-(3-methyl-4-pyridyl)anilino]-3-cyclobutene-1,2-dione**

In a manner similar to that of Example 1, 4-(3-aminophenyl)-2-methylpyridine (0.55 g) and 3-amino-4-ethoxy-3-cyclobutene-1,2-dione (0.42 g) gave 0.28 g of the title compound, mp 205-208°C (from dimethylformamide).

**Example 6****3-Amino-4-[3-(2-oxazolyl)anilino]-3-cyclobutene-1,2-dione**

In a manner similar to that of Example 1, 2-(3-aminophenyl)oxazole (0.50 g) and 3-amino-4-ethoxy-3-cyclobutene-1,2-dione (0.44 g) gave 0.56 g of the title compound, mp 312-314°C (from dimethylformamide).

**Example 7****3-Amino-4-[3-(4-pyridyl)anilino]-3-cyclobutene-1,2-dione**

(a) A stirred mixture of 3-nitrophenylboronic acid (2.00 g), 4-bromopyridine hydrochloride (1.56 g), bis(diphenylphosphino)butanepalladium(II) chloride (0.48 g), sodium bicarbonate (2.69 g), water (30 ml) and 1,2-dimethoxyethane (100 ml) was heated under reflux for 3 hours. The cool mixture was added to water (300 ml) and extracted with chloroform (3 x 150 ml), and the combined organic extracts washed with water and brine, dried (MgSO<sub>4</sub>), charcoaled and filtered. The solvent was evaporated to give a residue which was purified by flash chromatography (silica, ether) to give 1.19 g of 4-(3-nitrophenyl)pyridine, mp 109-110.5°C (from acetone/hexane).

(b) A solution of the above nitro compound (1.18 g) in ethanol (30 ml) was shaken with 10% palladium on carbon (0.2 g) under hydrogen (50 psi) for 2.5 hours. Evaporation of the filtered solution gave a solid residue which was recrystallised from ethanol/40-60° Pet. ether to give 0.81 g of 4-(3-aminophenyl)pyridine, mp 167.5-168°C.

(c) In a manner similar to that of Example 1, the above amino compound (0.50 g) and 3-amino-4-n-butoxy-3-cyclobutene-1,2-dione (0.50 g) gave 0.50 g of the title compound, mp 297-300°C dec. (from dimethylformamide).

**Example 8****3-Amino-4-[3-(3-pyridyl)anilino]-3-cyclobutene-1,2-dione**

(a) In a manner similar to that of Example 7(a), 3-nitrophenylboronic acid  
5 (2.00 g) and 3-bromopyridine (1.26 g) gave 1.22 g of 3-(3-nitrophenyl)pyridine, mp 98.5-101°C (from acetone/hexane).

(b) A stirred mixture of the above nitro compound (1.22 g), stannous  
chloride dihydrate (6.5 g), conc. hydrochloric acid (6.5 ml) and ethanol (12.5 ml) was  
heated under reflux for 3.5 hours. Most of the ethanol was evaporated under reduced  
10 pressure and the residue made alkaline with 40% sodium hydroxide solution. The mixture  
was extracted with toluene (3 x 20 ml) and the combined organic extracts washed with  
water, dried (MgSO<sub>4</sub>) and evaporated to give a residue which was recrystallised from  
chloroform/40-60° Pet. ether to give 0.92 g of 3-(3-aminophenyl)pyridine, mp 75-76°C.

(c) In a manner similar to that of Example 1, the above amino compound  
15 (0.51 g) and 3-amino-4-ethoxy-3-cyclobutene-1,2-dione (0.42 g) gave 0.45 g of the title  
compound, mp 256-258°C (from methanol).

**Example 9****3-Amino-4-[3-(2-pyridyl)anilino]-3-cyclobutene-1,2-dione**

(a) In a manner similar to that of Example 7(a), 3-nitrophenylboronic acid  
20 (1.45 g), 2-bromopyridine (1.26 g) and tetrakis(triphenylphosphine)palladium(0) (0.50 g)  
gave 0.92 g of 2-(3-nitrophenyl)pyridine, mp 71.5-73°C (from ethanol).

(b) In a manner similar to that of Example 7(b), the above nitro compound  
(0.92 g) gave 2-(3-aminophenyl)pyridine (0.50 g) as a colourless oil.

(c) In a manner similar to that of Example 1, the above amino compound  
25 (0.50 g) and 3-amino-4-n-butoxy-3-cyclobutene-1,2-dione (0.50 g) gave 0.50 g of the title  
compound, mp 300-303°C dec. (from dimethylformamide/water).

**Example 10****3-Amino-4-[3-(2-thienyl)anilino]-3-cyclobutene-1,2-dione**

(a) In a manner similar to that of Example 7(a), 3-nitrophenylboronic acid  
(2.00 g) and 2-bromothiophene (1.30 g) gave 0.69 g of 2-(3-nitrophenyl)thiophene, mp  
70-72°C (from ether).

(b) In a manner similar to that of Example 8(b), the above nitro compound  
35 (0.69 g) and stannous chloride dihydrate (3.6 g) gave 0.43 g of 2-(3-aminophenyl)-  
thiophene, mp 30.5-32°C.

(c) In a manner similar to that of Example 1, the above amino compound (0.42 g) and 3-amino-4-ethoxy-3-cyclobutene-1,2-dione (0.34 g) gave 0.35 g of the title compound, mp 297-299°C dec. (from dimethylformamide/water).

## 5 Example 11

### 3-Amino-4-[3-(3-thienyl)anilino]-3-cyclobutene-1,2-dione

(a) In a manner similar to that of Example 7(a), 3-nitrophenylboronic acid (1.45 g), 3-bromothiophene (1.30 g) and tetrakis(triphenylphosphine)palladium(0) (0.50 g) gave 1.46 g of 3-(3-nitrophenyl)thiophene, mp 70.5-72.5°C (from ether/hexane).

10 (b) In a manner similar to that of Example 8(b), the above nitro compound (0.72 g) and stannous chloride dihydrate (3.75 g) gave 0.38 g of 3-(3-aminophenyl)thiophene, mp 86-88°C.

(c) In a manner similar to that of Example 1, the above amino compound (0.37 g) and 3-amino-4-n-butoxy-3-cyclobutene-1,2-dione (0.36 g) gave 0.37 g of the title  
15 compound, mp 304-307°C dec. (from dimethylformamide/water).

## Example 12

### 3-Amino-4-[3-(2-thianaphthenyl)anilino]-3-cyclobutene-1,2-dione

(a) In a manner similar to that of Example 7(a), 3-nitrophenylboronic acid  
20 (2.20 g), 2-bromothianaphthene (2.81 g) and tetrakis(triphenylphosphine)palladium(0) (0.25 g) gave 1.19 g of 2-(3-nitrophenyl)thianaphthene, mp 158-159°C (from acetone).

(b) In a manner similar to that of Example 8(b), the above nitro compound (1.18 g) and stannous chloride dihydrate (5.0 g) gave 0.45 g of 2-(3-aminophenyl)thianaphthene, mp 146-147°C.

25 (c) In a manner similar to that of Example 1, the above amino compound (0.44 g) and 3-amino-4-ethoxy-3-cyclobutene-1,2-dione (0.33 g) gave 0.37 g of the title compound, mp 318-321°C dec. (from dimethylformamide/water).

## Example 13

### 30 3-Amino-4-[3-(5-pyrimidyl)anilino]-3-cyclobutene-1,2-dione

(a) In a manner similar to that of Example 7(a), 3-nitrophenylboronic acid (2.00 g) and 5-bromopyrimidine (1.27 g) gave 1.16 g of 5-(3-nitrophenyl)pyrimidine, mp 159-160.5°C (from acetone).

(b) In a manner similar to that of Example 7(b), the above nitro compound  
35 (0.91 g) gave 0.65 g of 5-(3-aminophenyl)pyrimidine, mp 165-167.5°C (from acetone/hexane).

(c) In a manner similar to that of Example 1, the above amino compound (0.51 g) and 3-amino-4-ethoxy-3-cyclobutene-1,2-dione (0.42 g) gave 0.51 g of the title compound, mp 288-290°C dec. (from dimethylformamide/water).

5 **Example 14**

**3-Amino-4-[3-(2-benzoxazolyl)anilino]-3-cyclobutene-1,2-dione**

In a manner similar to that of Example 1, 2-(3-aminophenyl)benzoxazole (0.49 g) and 3-amino-4-ethoxy-3-cyclobutene-1,2-dione (0.33 g) gave 0.25 g of the title compound, mp 330-332°C dec. (from dimethylformamide/water).

10

**Example 15**

**3-Amino-4-[3-(2-benzimidazolyl)anilino]-3-cyclobutene-1,2-dione**

In a manner similar to that of Example 1, 2-(3-aminophenyl)benzimidazole (0.52 g) and 3-amino-4-ethoxy-3-cyclobutene-1,2-dione (0.36 g) gave 0.35 g of the title compound, mp >320°C (from dimethylformamide/water).

15

**Example 16**

**3-Amino-4-[3-(2-indolyl)anilino]-3-cyclobutene-1,2-dione**

In a manner similar to that of Example 1, 2-(3-aminophenyl)indole (0.48 g) and 3-amino-4-ethoxy-3-cyclobutene-1,2-dione (0.33 g) gave 0.22 g of the title compound, mp ca. 335°C dec. (from dimethylformamide/water).

20

**Example 17**

**3-Amino-4-(3-phenyl)anilino-3-cyclobutene-1,2-dione**

(a) In a manner similar to that of Example 7(b), 3-nitrobiphenyl (2.48 g) gave 1.77 g of 3-aminobiphenyl, mp 27.5-28.5°C.

25

(b) In a manner similar to that of Example 1, 3-aminobiphenyl (0.51 g) and 3-amino-4-ethoxy-3-cyclobutene-1,2-dione (0.42 g) gave 0.33 g of the title compound, mp 300-301°C (from dimethylformamide/water).

30

**Example 18**

**3-Amino-4-[3-(2-hydroxyphenyl)anilino]-3-cyclobutene-1,2-dione**

(a) A stirred mixture of 2-bromophenol (5.19 g), 4-methoxybenzyl chloride (4.70 g), potassium carbonate (4.15 g) and acetone (30 ml) was heated under reflux for 8

hours. The cool mixture was evaporated under reduced pressure and the residue was mixed with water (60 ml) and ether (60 ml) and shaken. The aqueous layer was extracted with ether (2 x 60 ml) and the combined extracts washed with 2M sodium hydroxide solution (20 ml) and water (20 ml), dried (MgSO<sub>4</sub>) and evaporated to give a solid residue which  
5 was recrystallised from ethanol to give 6.18 g of 1-bromo-2-(4-methoxybenzyloxy)-benzene, mp 87-90°C.

(b) In a manner similar to that of Example 7(a), 3-nitrophenylboronic acid (1.09 g), 1-bromo-2-(4-methoxybenzyloxy)benzene (1.76 g) and tetrakis(triphenylphosphine)palladium(0) (0.20 g) gave 1.34 g of 2-(4-methoxybenzyloxy)-3'-nitrobiphenyl,  
10 mp 99.5-100.5°C (from acetone/ether).

(c) In a manner similar to that of Example 7(b), the above nitro compound (0.86 g) gave 0.29 g of 2-hydroxy-3'-aminobiphenyl, mp 158-161°C.

N.B.: It is possible to terminate this reaction after adsorption of 3 moles of hydrogen to give 2-(4-methoxybenzyloxy)-3'-aminobiphenyl, mp 68-70°C (from ether/hexane).

(d) In a manner similar to that of Example 1, 2-hydroxy-3'-aminobiphenyl (0.28 g) and 3-amino-4-n-butoxy-3-cyclobutene-1,2-dione (0.26 g) gave 0.19 g of the title compound, mp 294-297°C dec. (from dimethylformamide/water).  
15

#### Example 19

##### 20 3-Amino-4-[3-(2-methoxyphenyl)anilino]-3-cyclobutene-1,2-dione

(a) In a manner similar to that of Example 7(a), 3-nitrophenylboronic acid, (1.45 g), 2-bromoanisole (1.50 g) and tetrakis(triphenylphosphine)palladium(0) (0.25 g) gave 0.39 g of 2-methoxy-3'-nitrobiphenyl, mp 67-8°C.

(b) In a manner similar to that of Example 7(b), the above nitro compound  
25 (0.39 g) gave 174 mg of 2-methoxy-3'-aminobiphenyl as an oil.

(c) In a manner similar to that of Example 1, the above amino compound (174 mg) and 3-amino-4-n-butoxy-3-cyclobutene-1,2-dione (148 mg) gave 146 mg of the title compound, mp 294-296°C (from dimethylformamide/water).

#### 30 Example 20

##### 3-Amino-4-[3-(3-hydroxy-2-pyridyl)anilino]-3-cyclobutene-1,2-dione

(a) A stirred mixture of 2,6-dibromopyridine (3.55 g), benzyl alcohol (1.63 g), potassium hydroxide (1.68 g), 18-Crown-6 (0.20 g) and toluene (25 ml) was heated under reflux for 30 minutes. The cool solution was washed with water and brine,  
35 dried (MgSO<sub>4</sub>) and evaporated to give an oil which was vacuum-distilled (Kugelrohr) to give 3.85 g of 2-benzyloxy-6-bromopyridine, bp 220-225°C / 1.0 mm.

(b) In a manner similar to that of Example 7(a), 3-nitrophenylboronic acid (1.09 g), 2-benzyloxy-6-bromopyridine (1.58 g) and tetrakis(triphenylphosphine)-palladium(0) (0.40 g) gave 0.95 g of 2-benzyloxy-6-(3-nitrophenyl)pyridine, mp 82.5-83.5 °C (from ether).

5 (c) In a manner similar to that of Example 7(b), the above nitro compound (0.94 g) gave 0.37 g of 2-(3-aminophenyl)-6-hydroxypyridine, mp 237-239°C (from methanol).

(d) In a manner similar to that of Example 1, the above amino compound (0.36 g) and 3-amino-4-n-butoxy-3-cyclobutene-1,2-dione (0.32 g) gave 0.46 g of the title  
10 compound, mp 320-322°C dec. (from dimethylformamide).

### Example 21

#### 3-Amino-4-[3-(2-imidazolyl)anilino]-3-cyclobutene-1,2-dione

(a) A stirred solution of methyl 3-nitrobenzimidate (7.57 g) and  
15 aminoacetaldehyde dimethylacetal (5.57 g) in methanol (20 ml) was heated under reflux for 24 hours. The cool solution was evaporated and the residue treated with water (9.5 ml) and conc. hydrochloric acid (21 ml). The mixture was heated (steam bath) for 15 minutes and evaporated under reduced pressure. Water (50 ml) was added to the residue and the insoluble solid filtered and washed with water. The filtrate was neutralized with potassium  
20 carbonate solution and the precipitated solid filtered and washed with water. The combined solids were charcoaled and recrystallised from ethanol to give 3.87 g of 2-(3-nitrophenyl)imidazole, mp 193-194.5°C.

(b) In a manner similar to that of Example 8(b), the above nitro compound (0.72 g) and stannous chloride dihydrate (4.25 g) gave 0.39 g of 2-(3-aminophenyl)-  
25 imidazole, mp 134-135.5°C.

(c) In a manner similar to that of Example 1, the above amino compound (0.38 g) and 3-amino-4-n-butoxy-3-cyclobutene-1,2-dione (0.40 g) gave 0.34 g of the title compound, mp >340°C (from dimethylformamide).

### 30 Example 22

#### 3-Amino-4-[6-(4-pyridyl)-2-pyridylamino]-3-cyclobutene-1,2-dione

A stirred solution of 2-amino-6-(4-pyridyl)pyridine (0.34 g) and 3-amino-4-n-butoxy-3-cyclobutene-1,2-dione (0.34 g) in pyridine (2 ml) was heated under reflux for 8 hours. The cool mixture was treated with water (15 ml) and the mixture stirred for 1 hour. The solid  
35 was filtered, washed with water, ethanol and ether, charcoaled and recrystallised from dimethylformamide to give 73 mg of the title compound, mp >340°C.



**Example 23****3-[3-(4-Pyridyl)anilino]-3-cyclobutene-1,2-dione**

- 5 A solution of 4-(3-aminophenyl)pyridine (0.81 g) and 3-n-butoxy-3-cyclobutene-1,2-dione (0.73 g) in ethanol (20 ml) was stirred at ambient temperature for 15 hours. The resultant precipitated solid was washed with methanol and ether and recrystallised from dimethylformamide to give 0.91 g of the title compound, mp 252-255.5°C.

**Example 24**

- 10 Pharmaceutical compositions for oral administration are prepared by combining the following :

		% w/w		
15	3-Amino-4-[4-(3-pyridyl)]anilino-3-cyclobutene-1,2-dione	0.5	3.0	7.14
	2% w/w Soya lecithin in soya bean oil	90.45	88.2	84.41
	Hydrogenated vegetable shortening and beeswax	9.05	8.8	8.45

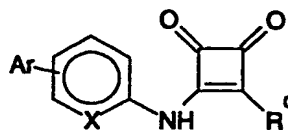
- 20 The formulations are then filled into individual soft gelatin capsules.

**Example 25**

- A pharmaceutical composition for parenteral administration is prepared by dissolving the title compound of Example 2 (0.02 g) in polyethylene glycol 300 (25 ml) with heating.
- 25 This solution is then diluted with water for injections Ph. Eur. (to 100 ml). The solution is then sterilised by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

# Claims

1. A compound of the formula (1) :



Formula (1)

- or a pharmaceutically acceptable salt thereof, wherein
- Ar is an optionally substituted aryl or heteroaryl ring selected from phenyl, naphthyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, imidazolyl, thienyl, oxazolyl, benzimidazolyl, benzoxazolyl, indolyl or thianaphthenyl,
  - X is CH or N;
  - R<sup>0</sup> is NR<sup>1</sup>R<sup>2</sup> or hydrogen; and
  - R<sup>1</sup> and R<sup>2</sup> are independently hydrogen or C<sub>1-6</sub>alkyl.
2. A compound according to claim 1 wherein Ar is phenyl.
  3. A compound according to claim 1 wherein Ar is 2-,3- or 4-pyridyl, 5-pyrimidyl, 2- or 4-imidazolyl, 2- or 3-thienyl, 2-oxazolyl, 2-benzimidazolyl, 2-benzoxazolyl, 2-indolyl or 2-thianaphthenyl.
  4. A compound according to any one of claims 1 to 3 wherein Ar is unsubstituted or substituted by at least one group selected from C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy or hydroxy.
  5. A compound according to any one of claims 1 to 4 wherein Ar is positioned ortho- or meta- to X.
  6. A compound according to any one of claims 1 to 5 wherein X is CH.
  7. A compound according to any one of claims 1 to 6 wherein R<sup>0</sup> is NR<sup>1</sup>R<sup>2</sup>.
  8. A compound according to claim 7 wherein R<sup>1</sup> is hydrogen and R<sup>2</sup> is hydrogen or C<sub>1-6</sub>alkyl.

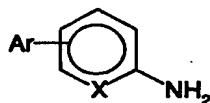
9. A compound according to claim 1 selected from :

- 3-amino-4-[4-(3-pyridyl)]anilino-3-cyclobutene-1,2-dione,  
3-amino-4-[3-(4-imidazolyl)anilino]-3-cyclobutene-1,2-dione,  
3-methylamino-4-[3-(5-methyl-4-imidazolyl)anilino]-3-cyclobutene-1,2-dione,  
5 3-dimethylamino-4-[3-(5-methyl-4-imidazolyl)anilino]-3-cyclobutene-1,2-dione,  
3-amino-4-[3-(3-methyl-4-pyridyl)anilino]-3-cyclobutene-1,2-dione,  
3-amino-4-[3-(2-oxazolyl)anilino]-3-cyclobutene-1,2-dione,  
3-amino-4-[3-(4-pyridyl)anilino]-3-cyclobutene-1,2-dione,  
3-amino-4-[3-(3-pyridyl)anilino]-3-cyclobutene-1,2-dione,  
10 3-amino-4-[3-(2-pyridyl)anilino]-3-cyclobutene-1,2-dione,  
3-amino-4-[3-(2-thienyl)anilino]-3-cyclobutene-1,2-dione,  
3-amino-4-[3-(3-thienyl)anilino]-3-cyclobutene-1,2-dione,  
3-amino-4-[3-(2-thianaphthenyl)anilino]-3-cyclobutene-1,2-dione,  
3-amino-4-[3-(5-pyrimidyl)anilino]-3-cyclobutene-1,2-dione,  
15 3-amino-4-[3-(2-benzoxazolyl)anilino]-3-cyclobutene-1,2-dione,  
3-amino-4-[3-(2-benzimidazolyl)anilino]-3-cyclobutene-1,2-dione,  
3-amino-4-[3-(2-indolyl)anilino]-3-cyclobutene-1,2-dione,  
3-amino-4-(3-phenyl)anilino-3-cyclobutene-1,2-dione,  
3-amino-4-[3-(2-hydroxyphenyl)anilino]-3-cyclobutene-1,2-dione,  
20 3-amino-4-[3-(2-methoxyphenyl)anilino]-3-cyclobutene-1,2-dione,  
3-amino-4-[3-(3-hydroxy-2-pyridyl)anilino]-3-cyclobutene-1,2-dione,  
3-amino-4-[3-(2-imidazolyl)anilino]-3-cyclobutene-1,2-dione,  
3-amino-4-[6-(4-pyridyl)-2-pyridylamino]-3-cyclobutene-1,2-dione, or  
3-[3-(4-pyridyl)anilino]-3-cyclobutene-1,2-dione,  
25 or a pharmaceutically acceptable salt thereof.

10. A compound according to any one of claims 1 to 9 for use as a medicament.

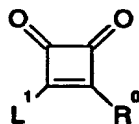
11. A pharmaceutical composition comprising a compound according to any one of claims 1 to 9 and a pharmaceutically acceptable carrier.

12. A process for the preparation of a compound of the formula (1) as defined in claim 1 or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of the formula (2) :



Formula (2)

with a compound of the formula (3) :



Formula (3)

wherein Ar, X and R<sup>0</sup> are as hereinbefore defined and L<sup>1</sup> is a leaving group, and thereafter optionally forming a pharmaceutically acceptable salt thereof.

13. The use of a compound according to any one of claims 1 to 9 in the manufacture of a medicament for inhibiting a calmodulin insensitive cyclic GMP phosphodiesterase.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 94/01921

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 5 C07D233/38 A61K31/135 A61K31/33 C07D233/24 C07D263/32 C07D333/20 C07D335/06 C07C225/20 C07D239/26 C07D263/56 C07D235/18 C07D209/14 C07D213/64 C07D213/74		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 5 C07D A61K C07C		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 108, no. 7, 15 February 1988, Columbus, Ohio, US; abstract no. 48712j, DAVIS, A. ET AL. 'Strategic approaches to drug design. II. Modeling studies on phosphodiesterase substrates and inhibitors.' see abstract * RN 112127-67-0 * & J. COMPUT.-AIDED MOL. DES. 1987,1(2),97-119 ---	1,13
A	EP,A,0 428 268 (SMITHKLINE & FRENCH LABORATORIES LTD) 22 May 1991 * page 2, line 1-5; claim 1 * --- ---	1,13
-/--		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "I" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "&" document member of the same patent family		
Date of the actual completion of the international search  2 September 1994		Date of mailing of the international search report  14. 09. 94
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. ( + 31-70) 340-2040, Tx. 31 651 epo nl, Fax: ( + 31-70) 340-3016		Authorized officer  Van Bijlen, H

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 94/01921

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 400 799 (SMITHKLINE & FRENCH LABORATORIES LTD) 5 December 1990 * page 2, line 1-8; claim 1 * ---	1,13
A	EP,A,0 395 328 (SMITHKLINE & FRENCH LABORATORIES LTD) 31 October 1990 * page 2, line 1-8; claim 1 * -----	1,13

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

PCT/EP 94/01921

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0428268	22-05-91	AU-B-	624536	11-06-92
		AU-A-	6390290	18-04-91
		JP-A-	3145466	20-06-91
-----				
EP-A-0400799	05-12-90	DE-D-	69005904	24-02-94
		DE-T-	69005904	05-05-94
		JP-A-	2295977	06-12-90
		US-A-	5290933	01-03-94
-----				
EP-A-0395328	31-10-90	AU-B-	623512	14-05-92
		AU-A-	5367490	01-11-90
		JP-A-	2295978	06-12-90
		US-A-	5118686	02-06-92
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